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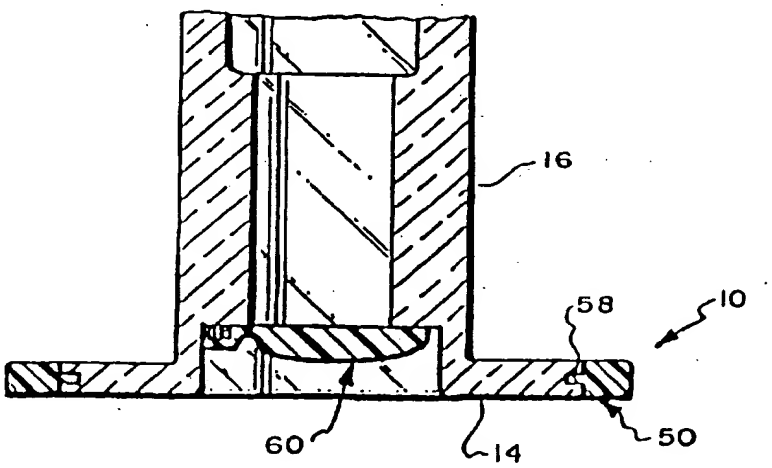
(54) Title: MEDICAL DEVICES HAVING MICROBIAL RESISTANT MATERIAL PROPERTIES



(57) Abstract

Microbial growth on the surface of a medical device such as a prosthetic and particularly a voice prosthesis (10) is inhibited by forming the prosthesis of or coating the surface with a layer of a fluoropolymer selected from a fluorocarbon polymer or a fluorosilicone polymer, particularly a perfluoroalkyl substituted siloxane such as methyl trifluoropropyl siloxane.

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Description

MEDICAL DEVICES HAVING MICROBIAL RESISTANT MATERIAL PROPERTIES

Technical Field

The present invention relates to microbial-resistant medical devices and, more particularly, this invention relates to a voice prosthesis having material properties which resist growth of microbial organisms.

Background of the Invention

Medical devices, particularly prosthetic devices which are used in environments where micro-organisms such as fungi or yeast are actively growing, can become covered with a microbial layer to the point where the function of the device is impaired. The fouled device must be cleaned or discarded.

Whenever a prosthesis is in contact with moisture in a hot, dark environment, the surfaces are subject to microbial growth, typically Candida Albicans. The microbial growth can interfere with the functioning of the prosthesis, requiring removal of the prosthesis for disposal or cleaning. The microbial growth is a persistent problem in the management and care of patients who have had their larynx removed and utilize a voice prosthesis.

There are several options for restoring speech to patients who have had their larynx removed. One procedure is to surgically create a puncture or fistula between the trachea and the esophagus. A trachea voice prosthesis containing a one-way valve such as a BLOM-SINGER® voice prosthesis is inserted into the tracheoesophageal fistula. The one-way valve protects the airway during swallowing but opens under positive pressure. The voice prosthesis, thus, permits a patient to divert air from the lungs into the esophagus and

out through the mouth. Speech is created during passage of air through the upper part of the esophagus.

The prosthesis maintains the fistula open, transfers air from the trachea to the esophagus for voice production and prevents esophageal leakage into the trachea during swallowing. The oral cavity which extends into the throat has a high microbial population. However, the prosthesis being in contact with moisture in a hot, dark environment is subject to growth of commonly found micro-organisms, typically Candida Albicans on the valve and the retaining flange. The microbial attack is currently being studied. The microbial attack, organisms and sequence of events are quite complex and are still undetermined. The microbial growth can interfere with function of the valve and can cause the flange to wrinkle and leak.

The current low pressure voice prosthesis can be removed by the patient every few days and can be replaced with a clean prosthesis. The removed prosthesis is soaked in hydrogen peroxide to remove the layer of yeast from the valve and flange. Some patients however, have difficulty managing frequent removal and reinsertion of the prosthesis. Others, who are physically handicapped are not able to remove, sterilize, or reinsert the prosthesis.

A longer dwelling, low pressure voice prosthesis has been developed that can remain in place in the tracheoesophageal fistula for many weeks or months, depending on the patient and conditions of use. The patient can confidently use the prosthesis for longer periods. The longer dwelling voice prosthesis is not removable by the patient and does not allow cleaning and soaking. Trips to a health care specialist to remove and replace the prosthesis are greatly extended providing increased comfort and lower cost to the patient.

Microbial growth on the valve can also cause distortion of the shape of the valve or form wrinkles in the body of the valve which prevents the valve from closing. Leaking also ap-

pears to be due to distortion of the valve body adjacent to the seat of the valve and to yeast growth on the seat. Forming the valve with an arcuate dome shape increased resistance to folding or bending of the valve. However, some valves still leaked after extended placement in a fistula.

List of Prior Art

Patent No.	Patentee
3,932,627	Margraf
4,054,139	Crossley
4,563,485	Fox, Jr. et al.
4,581,028	Fox, Jr. et al.
4,612,337	Fox, Jr. et al.
4,615,705	Scales et al.
5,019,096	Fox, Jr. et al.

Statement of Prior Art

Margraf discloses the use of a silver-heparin-allantoin complex to a form non-thrombogenic, self sterilizing surface on prosthetic valves or arterial grafts. The complex can be coated or impregnated into the surface of the valve or graft.

Crossley coats the surface of an urinary tract catheter with Ag or Ag compounds by dispersing silver or its compound in resin. The surface is abraded to expose the silver material. The coating contains 10% by weight of silver (col 4, line 10). The coating can be extremely thin such as those deposited by electroless deposition (col 4, lines 16-18).

Fox, Jr. et al., 4,563,485 discloses use of silver norfloxacin or silver perfloxacin to render muscular graft prosthesis formed from resins such as silicone infection resistant.

Fox, Jr. et al., 4,581,028 utilizes silver metal salts of sulfonamides or other antimicrobials for the same purpose.

Fox, Jr. et al., 4,612,337 discloses and claims a method of preparing an infection resistant material by solvent impregnation of the material with a silver salt and another

compound and reaction in situ to form a silver salt.

Scales et al., 4,615,705 provides a bioerodible silver coating on the surface of endoprosthetic orthopaedic implants to render the surface antimicrobial.

Fox, Jr. et al., 5,019,096 discloses the use of a complex of a silver salt and chlorhexidine to add antimicrobial properties to biomedical polymers such as silicones.

Dorland's Illustrated Medical Dictionary discloses the use of silver picrate to locally treat monilia (Candida) infections of the vagina.

U.S. Patent No. 5,314,470 discloses a soft voice prosthesis which includes a stiffening ring 14 inserted into a groove in the body of the prosthesis. Though the ring stiffens the body adjacent the valve it does not prevent distortion of the body by muscular movement or distortion of the valve by growth of yeast.

Statement of the Invention

The invention relates to the discovery of a polymer material that can be used to form the microbial resistant properties for medical devices, especially prosthetic devices exposed to Candida Albicans in oral and tracheal environments. The material is safe and effective and is neither toxic, inflammatory nor irritating to adjacent tissues. The material can be plastic or elastomeric, as required, depending on compounding. Preferred materials are liquid polymers that can be cast or molded or thermoplastic polymers that can be softened to be shaped by molding or extrusion.

The microbial resistant materials of the invention are formed from polymers containing a plurality of fluorine atoms pendant from the polymer backbone. The polymer material can have a carbon backbone or a siloxane backbone. The fluorine atoms can be directly attached to the polymer backbone or can be attached to a group pendant from the backbone such as a group containing 1 to 20 carbon atoms, suitably an alkyl

group, aryl group, cycloakyl group or combinations thereof. The polymer of the invention can contain segments of other polymers or can be mixed with other polymers to modify or adjust properties.

The mechanism for inhibiting growth of yeast is not understood though it is believed to be a function of the smoothness and inertness of the surface of these polymers inhibiting attachment and growth of a colony of yeast cells. The fluorine atom may also exhibit toxicity to the yeast cells and contributes inertness to the polymer. The polymer contains at least 0.1% by weight of fluorine in the polymer, preferably from 1 to 10% by weight.

Common, commercial fluorine-containing polymers are fluorocarbon, fluorinated silicone polymers and fluorinated acrylate polymers. Silicone based materials are preferred since they are more processable to form a prosthesis with elastomeric properties. Silastic fluorosilicones are known to have good resistance to acids, alkalis, solvents, oils, alcohols, esters and ketones. Fluoralkyl substituted silicones have shown the best yeast resistance to date. Further testing of trifluoro-alkyl substituted siloxanes is proceeding.

These and many other features and attendant advantages of the invention will become apparent as the invention becomes better understood by reference to the following detailed description when considered in conjunction with the accompanying drawings.

Brief Description of the Drawings

Figure 1 is a schematic view of a voice prosthesis installed in a tracheoesophageal fistula;

Figure 2 is a partial view in section of a voice prosthesis with hinged valve;

Figure 3 is a view in section of a voice prosthesis containing an internal rigid cartridge; and

Figure 3A is an enlarged sectional view of a portion of Figure 3 for purposes of clarity.

Detailed Description of the Invention

The invention will be illustrated by a long-dwelling voice prosthesis, though it is applicable to any prosthetic or medical device disposed in a body cavity having an environment conducive to growth of micro-organisms such as Candida Albicans.

Referring now to Figure 1, a voice prosthesis 10 is shown inserted into a fistula 62 with the front flange 14 engaging the outer wall 64 of the trachea and the rear flange 16 engaging the wall 66 of the esophagus. The body 12 of the prosthesis 10 prevents the fistula 62 from closing. The prosthesis also contains a valve 60 as shown in Figure 2. The valve 60 is preferably separately molded and has a flap which is attached to the prosthesis 10. The valve 60 contains radiopaque pigment and the flange 14 may contain a radiopaque ring 50 for visualization of the valve 60 and concentric ring 50 after the prosthetic device has been seated in the fistula as disclosed in U.S. Patent No. 5,480,432, the disclosure of which is expressly incorporated herein by reference. At least the valve 60 is formed of the yeast resistant material of the invention or contains a thin coating 63 formed on the surface of the valve 60.

The prosthesis 10 can further contain an internal, rigid cartridge 18 to reinforce the body of the soft prosthesis as shown in Figures 3 and 3A and as disclosed in copending application Serial No. 08/559,210 filed November 13, 1995, the disclosure of which is expressly incorporated herein by reference.

The voice prosthesis 90 contains an improved cartridge 92. The front flange 94 of the cartridge 92 has a bevel 96 so that it is easier to move the front flange 94 past the boss 98

on the body 100 of the device. A groove 102 may be provided in the inner wall 101 of the body 100 adjacent the front of the boss 98. The groove 102 preferably has a beveled front face to receive and lock the flange 94 as it snaps into the groove 102. The boss 98 seats between the flanges 94 and 110 and the wall segment 139 of the cartridge 92.

Another feature of the cartridge 92 of the invention is the placement of the adhesive cavity 106 in the rear of the rear flange 110 such that it communicates with the slot 112. The valve 15 and cartridge 92 can be preassembled before the cartridge is inserted into the flexible body 100. The tab 56 is inserted through slot 112 in the flange 110 into the cavity 106. Adhesive 70 can be placed into the cavity from the rear opening 113 of the cavity 106. There is no need for a cavity in the flexible body which would weaken the body and could provide a site for failure during flexure of the soft elastic body adjacent the hard flange.

The body 100 can also contain an elongated hood 120 placed rearward of the rear flange 110 to further protect the valve 15 from failing.

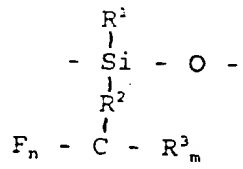
The microbial resistant surface of the invention may eliminate or reduce the need to utilize a thick domed valve and a thicker, stiffer rear flange. Since the growth of a thick layer of yeast will be inhibited, warping of the valve is reduced or eliminated. The microbial resistant surface can be provided by coating or laminating a layer of yeast resistant polymer onto the exposed surfaces of the valve and body of the prosthesis.

The microbial resistant surface is formed of a polymer having a minimum thickness to inhibit microbial growth, generally at least 0.005 inches in thickness and usually from 0.01 to 0.3 inches in thickness. A layer of microbial resistant polymer can be coated onto the surface from solutions or dispersions of the polymer, can be formed on the surface by polymerization of monomers in situ, or by curing liquid

prepolymers on the surface of the prosthesis. The layers can also be laminated to the surface by adhesive or by heat. In the case of certain elastomeric polymers that have the appropriate physical properties for use as a prosthesis, the prosthesis may be formed from the microbial resistant polymer.

Suitable fluorocarbon polymers for forming the yeast resistant surface are high fluorine content fluorocarbons in which at least 20% of the chain carbon atoms are substituted with fluorine. Representative commercially available polymers are polytetrafluoroethylene, chlorotriflouroethylene, polyvinylidene fluoride, and copolymers such as copolymer of chlortrifluoroethylene and vinylidene fluoride, copolymer of hexafluoropropylene and vinylidene fluoride, perfluoro butyl acrylate.

Voice prosthesis are usually formed from elastomers in order to better conform to and seal the device in a fistula. A preferred class of fluorinated elastomer are based on fluoroalkyl substituted siloxanes having a repeating unit of the formula:



where R^1 is a group containing 1 to 10 carbon atoms such as alkyl, suitably methyl, aryl such as phenyl or aralkyl, alkaryl, R^2 is a divalent group containing 1 to 8 carbon atoms such as ethylene and R^3 is a group containing 1 to 8 carbon atoms selected from alkyl, aryl, aralkyl or alkaryl and $n + m = 3$ and $n = 2$ or 3. The molecular weight can be from 20,000 to 5,000,000, generally from 50,000 to 1,000,000. Replacement of the methyl group with a longer alkyl chain modifies the properties of the siloxanes. The activation energy for viscous flow and the rate of change of viscosity with temperature and pressure increase. Compatibility with organic compounds

increase and lubricity improves. Methyl trifluoropropyl silicone has a solubility parameter of about 9.5 compared to about 7.5 for dimethyl silicone. A commercially available fluorosilicone elastomer is methyl trifluoropropyl siloxane having the following physical properties suitable for a voice prosthesis.

FLUOROSILICONE ELASTOMER DUROMETER

PHYSICAL PROPERTIES:	SPECIFICATION
DUROMETER, SHORE A	30-80
TENSILE STRENGTH, LB/SQ IN.	750 MINIMUM
ELONGATION, %	300 MINIMUM
TEAR STRENGTH, LB/IN.	90 MINIMUM
SPECIFIC GRAVITY	1.1 - 1.5

SLABS USED FOR TESTING WERE PRESS CURED 10 MINUTES AT 350 DEGREES F. POST CURED 4 HOURS AT 400 DEGREES F.

Methyl trifluoropropyl siloxane elastomers are formed from polymerizable compositions containing a small amount 0.05 to 5% of an unsaturated copolymerizable monomer such as:

$CH^3 - SiO - CH^2 = CH$

Fluorosilicone raw gums can be prepared from anionic, non-solvent reactions of the corresponding cyclosiloxanes. They are generally compounded with fumed and precipitated fillers, hydroxy-containing low viscosity silicone oils and readily available peroxides.

The fluorosilicone elastomers are generally polymerized by free radical initiated polymerization using free radical agents such as benzoyl peroxide or bis(2,4 - dichlorobenzoyl) peroxide.

During vulcanization, the only significant volatile species formed are by-products of the peroxides. No fluorine-containing by-products are formed. Typical cure cycles are 5-10 minutes at 116-171° C depending on the choice of peroxide. With most fluorosilicones (as well as with other fluoroelastomers) a post-cure of 4-24 hours at higher temperature is

recommended to maximize long term thermal aging properties. This post cure completes reactions of the unsaturated side groups, resulting in increased tensile strength and higher cross-link density.

Fluorosilicone elastomers can be molded by any of the conventional types of methods employed in the industry. Compression molding is the most widely used method and is ideal for a great many fabrications at temperatures between 116-171° C and pressure of MPa 5.5-10.3 (psi 800-1500). Injection molding is becoming increasingly important for high production operations and generally requires higher temperatures and pressures then compression molding. Transfer molding is particularly useful for molding complex parts in multicavity presses.

Since corrosive gases are not liberated during the molding process, a variety of metals such as brass, steel, copper, stainless steel, etc. can be used in making the mold. Where dimensional accuracy of molded parts is very important the design of the mold must allow for shrinkage of the parts. Linear shrinkage of most fluorosilicones is 2.5-3.5%.

It is usually necessary to use a mold release agent when molding fluorosilicone elastomers, though it may not be needed for chrome-plated or highly polished mold surfaces. A light coat of 1-3% solution of Duponol® WAQ in water or isopropyl alcohol, or a 2-5% solution of household detergent in water will prevent sticking.

A clinical trial (in vivo) was conducted to determine the effectiveness of fluorosilicone resins such as methyl trifluoropropyl siloxane in inhibiting microbial growth and prolonging the useful life of a voice prosthesis. The trail is still in progress with additional patients being added as available.

Of the seven patients in the trial, two have recently been added and no data is available. In two other patients, the fluorosilicone voice prosthesis was removed from the

patient for medical reasons not related to the study. The three remaining patients had excellent results with the fluorosilicone material as the body prolonged the useful life of the voice prosthesis for one patient from 23 days to 140 days or an additional 117 days. The other patients experienced increases in prosthesis life of 130 and 153 days respectively. In general the fluorosilicone material increased the life expectancy of the prosthesis by an average of 133 days or 281%. These results have not been optimized and greater improvements are expected in the future. The microbial growth is diminished and redirected to prevent leakage of the valve and thereby increase the life of the prosthesis.

Voice prosthesis formed with microbial resistant polymer surfaces will be able to be used for much longer periods without the need to remove the prosthesis for cleaning. The prosthesis can be made with thinner valves, body and flanges since there is no need to be as stiff and rigid to avoid bending and wrinkling due to growth of Candida Albicans or other microorganisms.

It is to be realized that only preferred embodiments of the invention have been described and that numerous substitutions, modifications and alterations are permissible without departing from the spirit and scope of the invention as defined in the following claims.

CLAIMS

1. A medical device resistant to growth of micro-organisms comprising:

an element of the device having external surfaces which will be exposed to an environment containing micro-organisms when placed on or into an animal cavity; and

a fluoropolymer capable of inhibiting growth of said micro-organisms comprising said surface.

2. A medical device according to claim 1 in which the device is a prosthesis and the surfaces inhibit growth of yeast.

3. A medical device according to claim 2 in which the yeast is Candida Albicans.

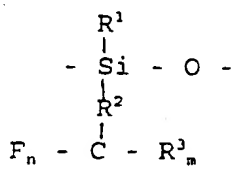
4. A medical device according to claim 2 in which the prosthesis is a voice prosthesis.

5. A medical device according to claim 1 in which the fluoropolymer is selected from the group consisting of fluorocarbon polymers and fluorosilicone polymers.

6. A medical device according to claim 5 in which the fluorocarbon polymer contains a carbon chain and fluorine atoms are attached to at least 20% of the available attachment sites on said chain.

7. A medical device according to claim 6 in which the fluorocarbon polymer is a polymer or copolymer of at least one monomer selected from the group consisting of tetrafluoroethylene, chlortrifluoroethylene, vinylidene fluoride or hexafluoroprolylene.

8. A medical device according to claim 5 in which the fluorosilicone polymer is formed from a monomer of the formula



where R^1 is a group containing 1 to 10 carbon atoms such as alkyl, suitably methyl, aryl such as phenyl or aralkyl, alkaryl, R^2 is a divalent group containing 1 to 8 carbon atoms such as ethylene and R^3 is a group containing 1 to 8 carbon atoms selected from alkyl, aryl, aralkyl or alkaryl and n + m = 3 and n = 2 or 3.

9. A medical device according to claim 8 in which the polymer is formed from a polymerizable mixture also containing a small amount of an addition polymerizable fluorine substituted comonomer.

10. A medical device according to claim 9 in which the comonomer is present in the mixture in an amount form 0.05 to 5% by weight.

11. A medical device according to claim 9 in which the monomer is methyl trifluoropropyl siloxane.

12. A method of inhibiting growth of yeast micro-organisms on the surface of a medical device comprising the steps of:

applying a fluoropolymer capable of inhibiting growth of said micro-organisms to said surface before exposing said surface to an environment containing said micro-organisms.

13. A method according to claim 12 in which the micro-organism is yeast and the fluoropolymer is selected from the group consisting of fluorocarbon polymer and fluorosilicone polymers.

14. A method according to claim 13 in which the fluorosilicone polymers are polymers of fluoroalkyl substituted siloxane in which the alkyl group contains 2 to 10 chain carbon atoms.

15. A method according to claim 14 in which the fluoroalkyl polymers are formed from trifluoroalkyl substituted siloxanes.

16. A method according to claim 15 in which the polymers are formed from trifluoropropyl substituted siloxanes.

Fig. 2

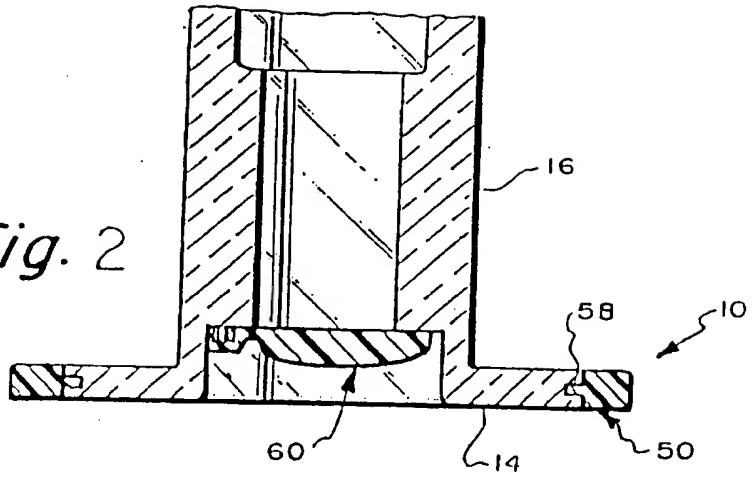


Fig. 1

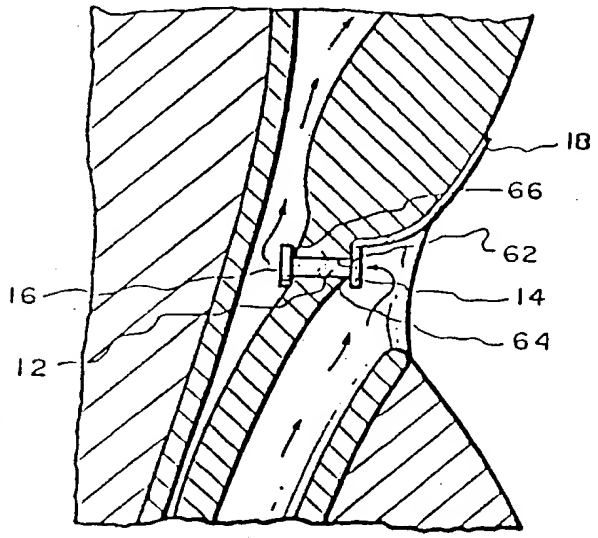


Fig. 3

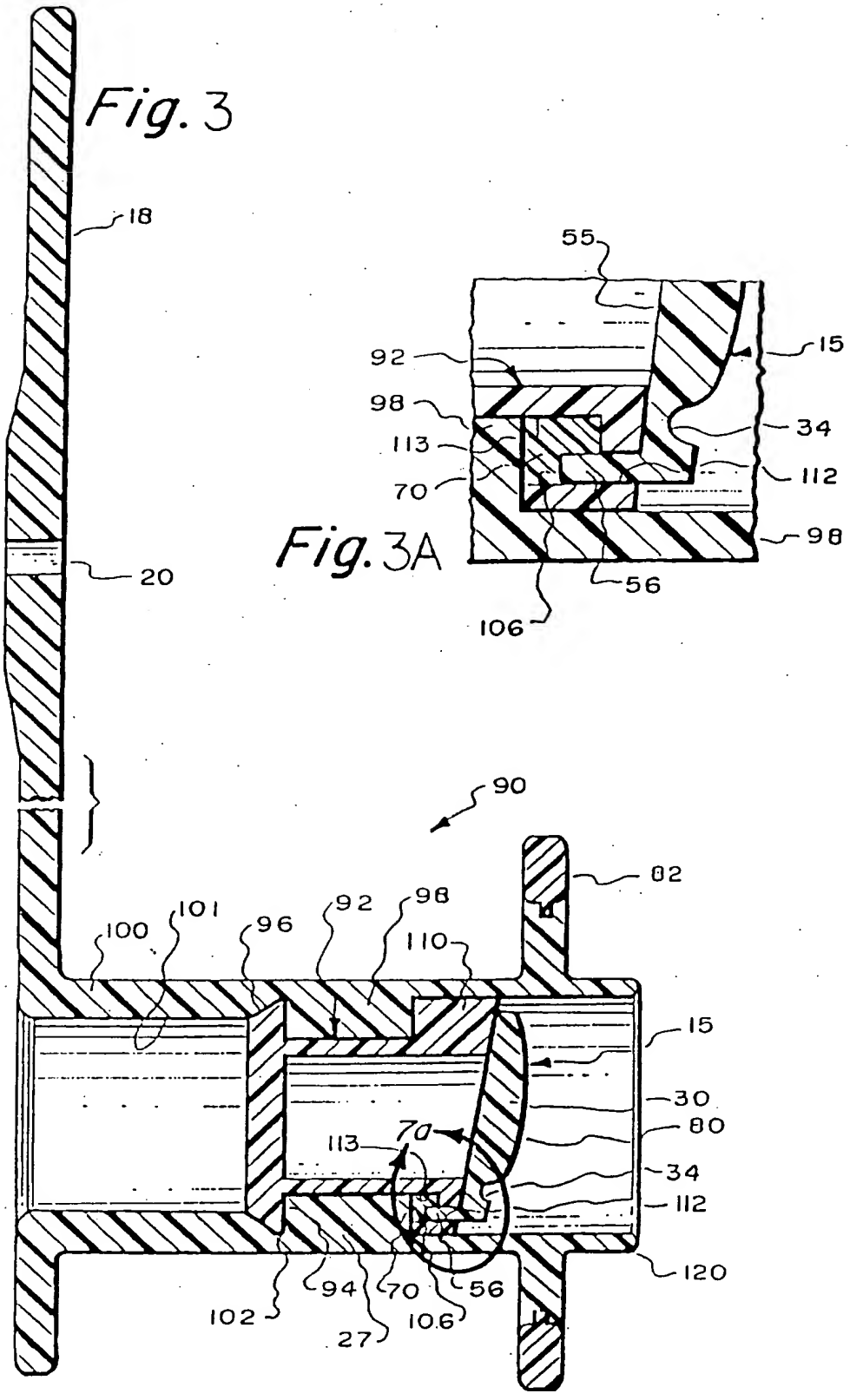

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Fig. 3A

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/15011

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61E 2/02
US CL :623/11
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. 623/11, 1, 12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,304,010 A (MANO) 8 DECEMBER 1981, COL. 5, LINES 18-21, CLAIMS 5 AND 14.	1-7
Y	US 5,529,820 A (NOMI ET AL.) 25 JUNE 1996, ENTIRE REFERENCE.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search
22 SEPTEMBER 1997

Date of mailing of the international search report
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